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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,407	12/26/2001	Larry Caldwell	TOPI-002CIP	3764

24353 7590 07/10/2009

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ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
07/10/2009	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/029,407
Filing Date: December 26, 2001
Appellant(s): CALDWELL ET AL.

Lynn J. Kidder
Bret E. Field
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 13, 2009 appealing from the Office action mailed November 04, 2008.

USPTO 892 and translation of the article for Pradalier et al. are attached to this examiner's answer.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

1) Pradalier et al., "Migraine and non-steroidal anti-inflammatory agents", Pathol Biol (Paris), 1992 Apr; 40(4): pp 397-405.

2) Cluff, "Migraine Treatment", International Association for the study of pain, Technical Corner from IASP Newsletter, 1999.

3)	5,667,799	Caldwell	09-1997
4)	5,318,960	Toppo	06-1994

(9) Grounds of Rejection

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

Claims 1-18 and 24-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of either one of the article by Pradalier et al.

or the article by Cluff, each article combined with both of US 5,667,799 ('799) and US 5,318,960 ('960).

Pradalier et al. teaches NSAID including ibuprofen, diclofenac and indomethacin having significant effect to treat migraine (see the provided abstract).

Cluff teaches NSAID including ketoprofen and ibuprofen as being beneficial as abortive treatment of migraine (see table 4, and the paragraph preceding table 4 of the provided article).

However, Pradalier and Cluff do not explicitly teach topical application of NSAID as instantly claimed.

US '960 (Toppo) teaches composition for pain relief comprising NSAIDs that when applied to the skin of the patient will deliver pain relieving substance directly to the afflicted area of the body, thus alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to the body at specific area of pain (abstract; co1.2, lines 5-9, 61-65). Examples of NSAID include indomethacin, ketoprofen, diclofenac, and ibuprofen (col.3, lines 50, 53, 56; col.6, lines 30, 58).

US '799 (Caldwell) teaches method for treatment of host suffering from headache pain with topical application of local anesthetic applied to keratinized skin proximal to target nerves associated with the headache pain, usually to the supraorbital or occipital regions of the head, so the drug penetrates the skin to block conduction in the target nerves and provides pain relief to the host (abstract; col.2, lines 41-67; col.3, lines 1-9; col.5, lines 18-29, claims). The drug applied topically in formulation comprising cream, plaster or patch (col.4, lines 12-15, 55-57, 66-67; col.5, lines 59-60). The method is

used to treat migraine headache (col.6, lines 15-16, 30-35). This method of application of headache pain relief composition to the skin proximal to target nerves associated with the headache is convenient method that is well tolerated by the patient and provides relief of pain shortly after application of the composition (col.6, lines 43-46). This method is improvement over systemic applications of NSAID to treat headache that provides undesired systemic side effects (col.1, lines 17-31).

Therefore, at the time of the invention, NSAIDs including those claimed by applicants were known in the art to be effective and beneficial to treat migraine as taught by Pradalier and Cluff, and NSAID were also known to be delivered topically at the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to the body at specific area of pain as taught by US '960, and furthermore, US '799 treated migraine by topical delivery of pain relief composition to keratinized skin proximal to target nerves associated with migraine headache, usually to the supraorbital or occipital regions of the head, so the drug penetrates the skin to block conduction in the target nerves and provides pain relief drug to the host.

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat migraine using NSAID as disclosed by any of Pradalier or Cluff, and deliver NSAID topically directly to the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to specific area of pain as taught by US '960, and further deliver NSAID to keratinized skin proximal to target nerves associated with migraine headache specifically to the

supraorbital or occipital regions of the head, so the drug penetrates the skin to block conduction in the target nerves and provides pain relief to the host by convenient well tolerated method as disclosed by US '799, with reasonable expectation of treating migraine headache by topically applying NSAID to keratinized skin proximal to target nerves associated with migraine headache to the supraorbital or occipital regions of the head to block conduction in the target nerves and effectively relief migraine without having undesired systemic side effects of NSAID wherein the method is convenient and well tolerated by the patient and provides relief of pain shortly after application of NSAID.

Regarding the amounts of NSAID recited in claims 29 and 30, the amount does not impart patentability to the claims, absent evidence the contrary. One having ordinary skill in the art the time of the invention would have determined the dose of the drug according to the severity of condition to be treated, patient age, and the specific formulation delivering the drug.

(10) Response to Argument

Appellants argue the rejected claims in groups as follows:

Group I: Claims 1-18, 24-26, 28, and 32-33

Group II: Claim 27

Group III: Claims 29-30

Group IV: Claim 31.

Accordingly, the examiner will answer the arguments in each group respectively.

Group I: Claims 1-18, 24-26, 28, and 32-33

Appellants submit argue that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 references fails to make obvious the rejected claims. Specifically, the combination of the references fail to teach or suggest the methods for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, consisting of topically applying a NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host, as is claimed. Appellants argue that the combined references do not teach or suggest all the elements of the rejected claims. Furthermore, Appellants found their clinical results unexpected and surprising, as they believed NSAIDs would not work topically and were only therapeutic if producing significant systemic levels. The rejected claims specify topical application, and "topical" drug products are understood by those of skill in the art to be products that produce their clinical effect by being applied to the skin, which subsequently interact with soft tissues and nerves underlying the keratinized skin where the drug is applied, and do not produce any significant systemic side effects.

In response to these argument, it is argued that the present invention as a whole is taught by the combined teachings of the prior art. At the time of the invention, NSAIDs including those claimed by applicants were known in the art to be effective and beneficial to treat migraine as taught by Pradalier and Cluff. NSAIDs were known to cause gastrointestinal side effects as taught by Pradalier. Further, NSAIDs were known

to be delivered topically at the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered to the body at specific area of pain as taught by Toppo. Contradictory to applicants' assertion that NSAIDs would not work topically and were only therapeutic if producing significant systemic levels. Additionally, Caldwell treats migraine by topical delivery of pain relief composition to keratinized skin proximal to the nerves associated with migraine headache, usually to the supraorbital (forehead) or occipital regions of the head, so the drug penetrates the skin to the target nerves associated with migraine and provides pain relief drug to the site of pain. In other words, "topical" drug products produce their clinical effect by being applied to the skin, which subsequently interact with soft tissues and nerves underlying the keratinized skin where the drug is applied. Therefore, all the elements of the claimed invention were taught by the cited prior art when combined.

In view of the state of the art, a person skilled in the art at the time of the invention aware of side effects caused by NSAIDs when given orally, and aware of their suitability for topical application to act locally without systemic effect, it is no difficult task for such a skilled artisan to deliver NSAIDs topically at the site of pain to obtain relief without gastrointestinal unwanted side effects.

Appellants argue that the rejected claims specify that a non-steroidal anti-inflammatory (NSAID) agent is the only active agent present in the topical formulation (i.e., there is no nerve blocking agent present). The claims also specify that the method is a method for ameliorating headache pain caused by migraine headache,

indomethacin responsive headache syndrome (IRH), a tension headache, or cluster headache (i.e., headaches caused by disturbances in the central nervous system), and not caused by musculoskeletal or peripheral nerve damage mechanisms.

In response to this argument, it is argued that the cause of migraine is inherent. Toppo teaches application of **NSAID as the only drug** to the specific area of pain to deliver pain relieving substances directly to the afflicted area of the body and does not teach inclusion of other nerve blocking agents. Caldwell teaches treating migraine by topical delivery of **single pain relief agent** to keratinized skin proximal to target nerves associated with migraine headache. Therefore, NSAIDS were disclosed to be capable to relief pain when applied to the site of pain as the only pain relief agent in the composition as taught by Toppo. Further, Toppo teaches that the NSAIDS are delivered directly to the afflicted area, so in case of headache, including migraine, NSAID will be delivered to the forehead and NSAIDS will follow the same pathway that should be inherent for the same drugs. The discovery of a new action underlying a known process does not make it patentable. *MEHL/Biophile*, 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. Also, it is irrelevant that the prior art observers did not recognize the property or function of the disputed claim; if the prior art inherently possessed that characteristic, it anticipates. See *Verdeegal Brothers, Inc. v. Union Oil Co. of Cal.,* 814 F.2d 628, 633, 2 U.S.P.Q.2d 1051, 1054 (Fed. Cir. 1987). This is believed to be applicable here because anticipation is the epitome of obviousness.

Appellants argue that the rejected claims require topically applying an anti-inflammatory effective amount of a topical NSAID formulation (not a nerve blocking agent) to a keratinized skin surface of the head, which work via a local anti-inflammatory mechanism (i.e., non-systemic), and is applied at a topical site which is not the site of the painful condition, the brain.

In response to this argument, it is repeated that Toppo teaches topical application of NSAIDS, and does not teach any nerve blocking agent in the topical composition and teaches application to skin that is naturally keratinized because the reference teaches the topical composition has the capacity to affect the individual surface skin cells and allow of passage of medicaments to the sub-dermal afflicted areas (abstract). Toppo does not teach removal of the epidermal layer to deliver the NSAIDS. Further, Caldwell teaches application of drugs to keratinized skin to treat migraine. Regarding appellants argument that the NSAIDS "applied at a topical site which **is not the site** of the painful condition, the brain", it is noted that this features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, even migraine headache originate in the brain, however, it manifests itself by pain in the forehead, occipital region and temple, and not pain in the brain. Toppo teaches application of the NSAIDS to the site of pain and Caldwell teaches application of NSAIDS to forehead, occipital region, and temple, which are the site of feeling the headache pain, and this what applicants have done.

Appellants further present the following argument:

A) The Appellants argue that the combination of the references does not render the claimed invention obvious because the combination of the cited references fails to teach or suggest each and every element of the claims.

Appellants argue that the combination of references fails to teach or suggest topically applying a topical NSAID formulation to a keratinized skin surface of the head to treat a headache of central nervous system origin, as claimed. The cited prior art references of Pradalier and Cluff disclose the general use of oral NSAIDs for the treatment of migraines. Pradalier and Cluff are silent with respect to topically applying a topical NSAID formulation as in the rejected claims. There is no teaching or suggestion in either reference of topical administration of NSAIDs. Accordingly,

Appellants further argue that Toppo is directed to NSAID compositions for relief of arthritis pain, where the area of pain experienced is also the exact site of inflammation and pain generation. Furthermore, headache and arthritis have distinct underlying pathophysiologies, with distinct diagnostic evaluations and therapies. The compositions of Toppo are delivered transdermally "directly to afflicted areas of the body", meaning the area of pain origin. Nowhere does Toppo describe applying a topical NSAID to the keratinized skin of the head, nor does Toppo describe use of the compositions to relieve headache of any kind. by applying a composition topically to the keratinized skin surface of the head, as in the current claims.

Appellants further argue that Caldwell is directed to a pain relief composition whose active agent is a local anesthetic which penetrates the keratinized skin surface so as to directly interact with underlying specific nerves resulting in nerve impulse conduction blockade in the stated target nerves. Local anesthetics are a specific and distinct class of drugs from NSAIDs. One of ordinary skill in the art would not extrapolate using the locally- applied anesthetic agent in Caldwell to the teaching of the other references to topically apply an NSAID for treatment of central headaches as in the current claims. Moreover, the site of application of the topical local anesthetic formulation in Caldwell is very specific such that the formulation patented will penetrate the skin in several specific sites as described in the patent so as to interact with the supraorbital nerve and/or suboccipital nerve and thereby resulting in a supraorbital nerve block and/or suboccipital nerve block, each of which are current methods of treating headache pain via needle injection.

In response to these argument, it is argued that the invention as whole is taught by the combination of the references. At the time of the invention, it would have been prima facie obvious to combine the references to arrive to the claimed invention in view of the cited references. Appellants attack the references individually, and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there

is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, at the time of the invention, NSAIDs including those claimed by applicants were known in the art to be effective and beneficial to treat migraine as taught by Pradalier and Cluff. Pradalier further recognized the gastrointestinal side effects caused by NSAIDS. Toppo overcome the gastrointestinal side effects of oral NSAIDS by topically applying such drugs at the site of pain to alleviate the side effects caused by systemic application and allowing NSAID to be delivered to the body at specific area of pain as taught by US Toppo and as desired by applicants. Furthermore, Caldwell treated migraine by topical delivery of pain relief composition to keratinized skin proximal to target nerves associated with migraine headache, supraorbital or occipital regions of the head, so the drug penetrates the skin and acts locally at the site of the pain and provides pain relief to the host. Toppo is not directed to treatment of arthritis as applicants assert. Toppo is directed to composition for transdermal delivery of pain reliving substances directly to the **afflicted areas of the body** (see col.1, lines 7-11; col.2, lines 5-10). Migraine headache manifests itself by pain in the forehead and occipital area or temple, and according to Toppo the topical NSAID formulation is applied to the sites where patient feels the pain. Caldwell is relied upon for teaching that migraine headache can be treated by applying the drug effective to treat migraine pain at keratinized skin of the **supraorbital area which is the forehead or the occipital area**, and not suboccipital as asserted by

appellants. Mechanism of action of the drug does not matter as long it is absorbed through the skin and contact the underlying tissues and exerts its action locally at tissues underlying the skin including nerves, blood vessels and muscles. Mechanism of action of drug is inherent, and as soon as the drug penetrates the skin it will follow its specific and characteristic pathway. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat migraine using NSAID as disclosed by any of Pradalier or Cluff, and deliver NSAID topically directly to the site of pain to alleviating the side effects caused by systemic application and allowing NSAID to be delivered precisely to specific area of pain as taught by Toppo, and further deliver NSAID to keratinized skin proximal to areas associated with migraine headache specifically to the supraorbital or occipital regions of the head, so the drug penetrates the skin to the underlying tissues and provides pain relief to the host by convenient well tolerated method as disclosed by Caldwell. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that the prior art suggest the combination or modification to

achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972).

Therefore, the combination of the references teaches applying a topical NSAID formulation to a keratinized skin surface of the head to treat a headache migraine, as instantly claimed. All the elements of the claimed invention are taught by the combination of the references as set forth.

B) The Appellants argue that the combination of the cited references fails to provide one of ordinary skill in the art with predicted success in the claimed invention.

The inventors of the present application found the unexpected and surprising results that one could treat the pain of central headaches including migraine headache, indomethacin responsive headache syndrome, a tension headache, or cluster headache, by applying a topical NSAID formulation to a keratinized skin surface of the head. Appellants argue that those of ordinary skill in the art would not have had a reasonable expectation of success in using a topical formulation of an NSAID applied to the keratinized skin surface of the head because (1) it was believed that the underlying pathophysiologic mechanism of migraines, indomethacin-responsive headaches, tension headaches, and cluster headaches were related to abnormalities deep within the brain; (2) it was known that topical formulations act locally and do not produce any significant drug levels in the systemic circulation nor in the brain; and (3) oral NSAIDs

were known to successfully treat headache symptoms only if clinically significant systemic blood levels were achieved.

In response to this argument, it is argued that the cited references show that it was well known in the art at the time of the invention to use NSAID to treat migraine, and also showed that NSAID can be applied at the site of pain, and further showed that migraine that has central origin is treated by topical application of the treating drug to the site of headache at the forehead, occipital or temporal area.

(1) Even if the pathophysiologic mechanism of migraine is deep in the brain, it was taught to be treated by topical application of pain relief agents to the forehead and occipital areas as taught by Caldwell.

(2) Although topical formulations act locally, and produce insignificant systemic effect that may affect he brain, however, topical formulation allows drug to reach to the underlying tissues including nerves, blood vessels, muscles, etc., and it relives pain through affecting such tissues underlying the skin, as taught by Toppo and Caldwell.

(3) Although oral NSAIDS are known to treat headache only when significant blood level is achieved, it is also known that NSAIDS have side effects when given orally and this side effects can be avoided by topical application as taught by Toppo.

Based on the disclosure by these references, an artisan of ordinary skill would have a reasonable expectation that a combination of these references would provide reasonable success. the combination of the references would have resulted into treating migraine using NSAIDS applied topically to the site of headache to keratinized skin. No patentable invention resides in combining old ingredients/method of known

properties/effect where the results obtained thereby are no more than the additive effect. See *In re Sussman*, 1943 C.D. 518; I*n re Huellmantel* 139 USPQ 496; *In re Crockett* 126 USPQ 186. It has been held that "When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR Int 'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. AG Pro, Inc.,* 425 U.S. 273,282 (1976)). "When the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." In addition, "To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ". Pp. 11-14. KSR INTERNATIONAL CO. v. TELEFLEXINC. ET AL. (2007).

It is well established that the claims are given the broadest reasonable interpretation during examination in light of the supporting disclosure as it would be interpreted by one of ordinary skill in the art, *In re Morris,* 127 F.3d 1048, 1054-55, 44 USPQ2d 1023,1027-28 (Fed. Cir. 1997); *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d

1359,1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). Further, it has been held that the words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004). In the present case, the reasonable interpretation of the claims would be treating migraine headache by topically applying NSAID to skin proximal to site associated with migraine headache which is the supraorbital or occipital regions of the head. The reasonable prediction from the combined teachings of the cited references would be treating migraine headache by topically applying to the site of headache, which is usually the forehead and the temporal area, a composition comprising NSAID, with a reasonable expectation of effective relief migraine headache without having undesired systemic side effects of NSAID wherein the method is convenient and well tolerated by the patient and provides relief of pain shortly after application of NSAID.

Appellants argue hat the examiner Dr. Newman's declaration showed indomethacin responsive headaches as representative of the class of NSAIDs. Furthermore, as discussed in the previously cited declaration by Dr. Galer, an indomethacin responsive headache is representative of the class of primary headaches, as are migraine, cluster, and tension headaches. In addition, the example cited in the original application demonstrated relief of migraine headache from topical diclofenac applied to the keratinized skin surface of the head.

In response to this argument, it is the position of the examiner that the declaration was directed to one specific species of NSAID indomethacin and the specification showed only diclofenac, each was provide in a specific formulation to provide skin penetration, and therefore, the declaration refer(s) only to the system described in the above referenced application and not to the individual claims of the application that not directed to the formulation that provides that applicants believe to be unexpected results. The unexpected results do not commensurate in scope with claims. The claims are directed to NSAID that encompasses many drugs that differ radically in their structure and behavior, and not all NSAID will have the same ability to penetrate the skin. Each NSAID drug requires different formulation to enable its topical delivery according to its nature. For example, hydrophilic drugs need different formulation than that needed by hydrophobic, and basic drugs need different formulation than that needed by acidic drugs. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

C) The Appellants argue that the Office has improperly combined Pradalier, Cluff, Toppo and Caldwell.

Appellants argue that the Office has used improper hindsight reasoning based on the disclosure in the Appellant's specification as the motivation to combine the references. The Examiner has not established that such reason would have been within the knowledge of one of ordinary skill in the art absent the Appellant's disclosure.

Nowhere, except in the Appellant's specification, is the teaching that a topically applied NSAID can be used to treat the head pain of a central headache such as migraine.

In response to this argument, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The reasons to apply NSAID topically is drawn from the prior art teachings because Pradalier recognized side effects of oral NSAID and Toppo realized that topical application to the site of the body where patient experience the pain in order to avoid such side effects. Caldwell further recognized applying pain relief composition to the target nerves associated with headache pain which are proximal to the forehead and occipital rejoin.

Appellants argue that there would be no reason that one of ordinary skill in the art at the time of the invention would have used a topical NSAID applied to the keratinized skin surface of the head to treat a headache caused by a disturbance in the central nervous system. Toppo does not teach to treat a central headache, for example, because this would mean applying the formulations of Toppo at a site of the affliction which is within the central nervous system, e.g., within the brain, not to a keratinized skin surface of the head, as in the rejected claims.

In response to this argument, it is repeated that migraine headache manifested by pain in the forehead and occipital area where the nerves associated with headache pain are located, as taught by Caldwell, and Toppo teaches application of topical formulation at the site where pain is felt. Migraine headache even it is generated in the brain, it is felt as headache in the forehead and occipital area, and not felt as pain in the brain. Toppo teaches treatment of pain at its site of manifestation because is not possible to apply topical composition to the deep tissues, such as joints, muscles or brain. This topically applied pain relief agents find their way to the deeper tissue flowing their specific physiological pathways and the penetrating the skin is facilitated by the formulation in which they are included.

Finally, in the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the claims would have been prima facie obvious within the meaning of 35 U.S.C. 103 (a). The invention as a whole is taught by the combined teachings of the cited references.

Group I I: Claim 27

Appellants repeat the argument as above, and further argue that claim 27 specifies that the headache pain is the result of indomethacin responsive headache syndrome and treated by topical formulation containing indomethacin. The cited prior art does not teach the limitations of claim 27.

Regarding claim 27, the combination of the references teach indomethacin for treating migraine as taught by Pradalier, and its topical application as taught by Toppo, col.3, line 50. One having ordinary skill in the art would have treated a symptom or disorder with the drug known to have effect on relieving such a symptom or disorder. Accordingly, indomethacin responsive headache obviously would be treated with indomethacin.

Group III: Claims 29-30

Appellants argue that claim 29 specifies amount of NSAID in the topical formulation ranges from about 0.1 to about 5.0% and claim 30 specifies from about 0.5 to about 3.% which not disclosed by the prior art.

However, those of ordinary skill in the art would have been readily optimized effective dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate dosage for treatment involving the above topical formulation would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, specially in view of the disclosure of Toppo that the topical doses of NSAIDS are greatly reduced more than the oral doses, e.g. ibuprofen is given in a dose 50 mg versus 1000-2400 mg orally. The concentration of NSAID in the topical formulation would have been determined by one having ordinary skill in the art based on patient population receiving the treatment and

severity of the condition to be treated. Additionally, concentration of the drug is controlled by the delivering topical formulation.

Group IV: Claim 31

Appellants argue that claim 31 specifies that the method of claim 1 results in no toxic side effects which are observed in system NSAID delivery mechanism, and the office has provided no valid reason to reject claim 31.

In response to this argument, it is argued that the prior art Pradalier and Toppo both recognized the side effects obtained from the oral administrations of NSAID, and further Toppo teaches avoidance of such side effects by topical application of the drugs. Therefore the limitation of claim 31 is implied and clearly taught by the cited prior art.

Finally, a conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969).

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter as a whole as defined by the claims would have been prima facie obvious within the meaning of 35 U.S.C. 103 (a).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Evidence Appendix

The examiner acknowledged the receipt of the evidence appendix filed with the appeal brief.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Isis A Ghali/

Primary Examiner, Art Unit 1611

Conferees:

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611

/Julie Burke/

Julie Burke, Manager TC1600